

mixed anhydride to the ester but with the exception of 2-keto acids the process was far from smooth. However, it was found fortuitously that on a micro-scale the presence of pyridine in a mixture with acetonitrile or water and alcohol results in immediate esterification. The alkyl chloroformates previously used for treating amines and phenols only suddenly became the general-purpose reagent.

The reaction mechanism is based on alcoholysis of the intermediate alkoxycarbonyl ester (the mixed anhydride). On the numerous applications published since 1990, the results for amino acids are especially impressive. It has been found that the alkyl group of the reagent and the alcohol need not be the same and different combinations lead to a variety of esters. In the field of metabolic profiling there is a report on simultaneous analysis of amino acids with other classes of compounds in serum without the need to isolate the analytes from the matrix. Profiling of urinary organic acids, for example, has been made possible after a simple sample pretreatment. Details are given in the review by Hušek (see Further Reading).

Conclusion

Silylating reagents were introduced in the 1960s and have been widely accepted as general purpose derivatizing reagents for GC, especially for polyfunctional compounds where derivatization is reduced to a one-step process. In the 1990s chloroformates were discovered as another family of powerful reagents which, in conjunction with a component of the medium, readily enable derivatization of many hydrogen-containing groups. They bring the additional advantage of derivatization in aqueous media, which often considerably simplifies the sample work-up. Last but not least, advanced alkylation/esterification procedures allow the simultaneous derivatization and extraction of analytes in sample matrices. The present

emphasis and future advances will focus on simplification and speed-up of sample preparation methods by process automation and combination of derivatization with work-up procedures.

See also: II/Chromatography: Gas: Detectors: Mass Spectrometry; Detectors: Selective. III/Acids: Gas Chromatography. **Amino Acids:** Gas Chromatography.

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Detectors: General (Flame Ionization Detectors and Thermal Conductivity Detectors)

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The two most common detectors for use after separation by gas chromatography (GC) are the flame ionization detector (FID) and the thermal conductivity detector (TCD). They are considered general (non-selective) detectors since they respond to virtually all

components that they encounter. In a strict sense of course this is not true, especially for the FID which does not respond to fixed gases or to gases commonly used as carrier gases. None the less, it is responsive to most components of interest and is clearly not selective in comparison to an electron-capture or nitrogen-phosphorus detector.

It is sometimes useful to denote detectors as ionizing or nonionizing depending on their mode of

action. By their very nature, ionizing detectors are destructive and the sample is not available for additional analysis. On the other hand, nonionizing detectors do not destroy the sample. Thus, two detectors may be set up in series, with the sample first encountering the nonionizing detector, and then directed to the ionizing detector. Of all the detectors available for use following separation by GC, the FID and the TCD are the leading examples of each of these types. These general-purpose detectors are in wide use following both packed column and capillary separations.

The material which follows is directed mainly to applications after capillary column separation, although some reference to packed columns is necessary in order to complete the discussion. Further details regarding packed column applications can be found by consulting the Further Reading section.

The Flame Ionization Detector

The FID was developed in 1958 by McWilliam and Dewar in Australia and almost simultaneously by Harley, Nell and Pretorius in South Africa and quickly became the detector of choice in commercial instrumentation. As an ionization detector, the FID responds readily to compounds that contain carbon and hydrogen and to a lesser extent to some compounds containing only carbon. It is unresponsive to water, air and most carrier gases. Because of its broad applicability and relative ease of operation, it is probably the most common detector in GC systems. The FID responds quickly and can be constructed with a small internal volume, which makes it especially well suited for capillary GC.

Response of an FID is due to the sample being burned in a fuel-rich mixture and producing ions. In the same process, electrons are produced. Either ions or electrons are collected at an electrode and produce a small current. Since there are virtually no ions present in the absence of sample, the baseline is stable and the current is easily converted to a voltage and amplified to produce a signal. The response to most hydrocarbons is about 0.015 C g^{-1} carbon.

As shown in **Figure 1**, the most often used configuration has the jet tip at approximately 200 V relative to the collecting electrode. For use with capillary columns, a smaller jet tip (c. 0.3 mm i.d. rather than the 0.5 mm used with packed column configurations) is utilized in order to increase detector sensitivity. The capillary column is usually inserted through the ferrule and then a few centimetres are broken off and discarded. Ideally, the column is positioned within 1–2 mm of the jet tip and column effluent enters the detector and mixes with hydrogen (fuel) and make-up gas without undue contact with metal surfaces. This

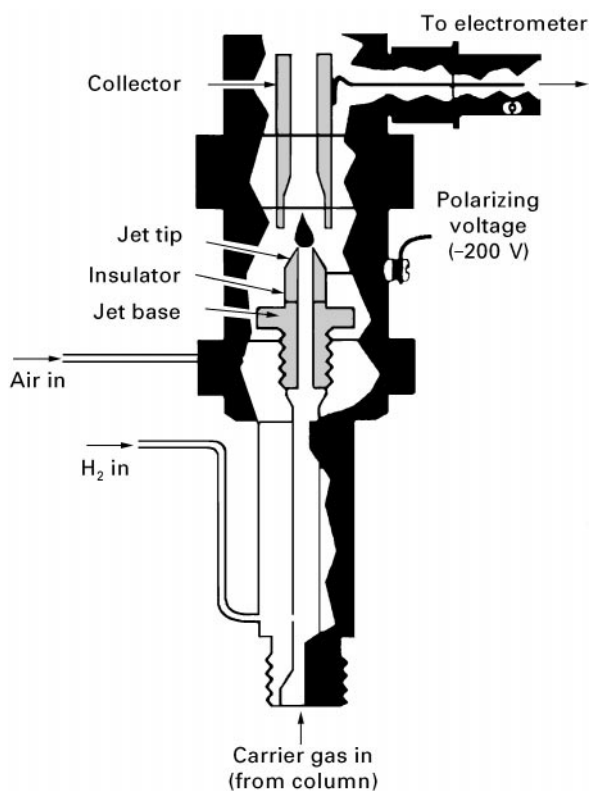


Figure 1 Cross-sectional diagram of a flame ionization detector.

mixture is combusted in an excess of air and the organic components are decomposed into ions. The ion chemistry of the diffusion flame has been studied by mass spectrometry. It appears that the ultimate positive charge carrier is H_3O^+ (or clusters of this with water molecules) resulting from charge transfer reactions from the initially formed ions (principally CHO^+). Thus the detector is often referred to as providing an 'equal per carbon response'.

This response to hydrocarbons allows one to quantify mixtures, for example from petroleum samples, without necessarily identifying each of the components individually present. With compounds other than hydrocarbons, the response is decreased when partially oxidized carbon atoms are present. This requires corrections to be made when the compounds contain, for example, oxygen, nitrogen or halogens. Either pure sample compounds or compounds of similar structure are used to establish appropriate response factors. Alternatively, the concept of effective carbon number has been updated to provide a model for the quantification of components in a complex organic mixture if they can be assigned to general functional group categories.

When used with narrow capillary columns, the FID usually requires a make-up gas for maximum sensitivity. The wider ($530 \mu\text{m}$) columns can be operated at

a higher carrier gas flow rate and may often be used without the additional make-up gas. For most operations the total flow rate (column + make-up) will be 20–60 mL min⁻¹. The fuel and air flow rates are maintained close to that recommended by the manufacturer – often 30–40 mL min⁻¹ for the hydrogen fuel and about 10-fold higher for the air. Under these conditions, the minimum detectable amount (MDA) of organic compounds is approximately 10–100 pg, depending on the structure. In addition, response is usually linear from the MDA to a concentration some 10⁷ times as great. (This higher limit is often beyond the loading capacity of narrow-bore capillary columns.) Flows to the detector can be adjusted while using standard samples containing the components of interest in order to obtain maximum response.

Water is a product of the combustion process producing the ions. Thus, the detector assembly must be kept hot in order to prevent condensation. A convenient guide is to have the detector 20–50° greater than the upper column temperature, but in no case lower than 150°C. Then water vapour, along with the other combustion gases, is swept out of the detector body. With most instruments, once the thermal environment of the detector has stabilized, temperature fluctuations are small and easily tolerated.

The FID is often described as a ‘forgiving’ detector since acceptable results are obtained even when the gas flows and other conditions are not optimized. None the less, some caution must be taken to avoid baseline drift, loss of sensitivity and the presence of spurious peaks. It is important to ensure that the gases employed are free from hydrocarbon impurities. Filters are available for this purpose. The flame itself is quite small and invisible, so checking for the presence of water vapour is the best approach to ensure that flame ignition has been successful. This can be done by holding a cold mirror above the outlet of the detector and observing condensation of the water vapour. Deterioration of performance of a properly operating FID is often the result of having used chlorinated solvents. Soot particles and the presence of HCl eventually lead to high and noisy baselines. The jet tip and collector electrode may have to be cleaned or, if badly corroded, replaced. Some spiking may be observed if portions of the polyimide coating are burned off the end of the capillary column.

The FID is mass flow-sensitive, meaning that the area response for a compound does not change as flow rate is varied. For quantitative work, appropriate response factors must be obtained, especially if a split injection mode is employed. When properly configured, a FID can respond to approximately 20 pg of each component eluting from a high resolution capillary column.

The Thermal Conductivity Detector

The TCD has long been a standby in packed column chromatography. It is a simple device, well suited to routine analyses where it is not necessary to detect low concentrations of components. It has been in use since the beginning of GC and has proven to be a rugged and dependable detector, in part because of the relatively simple electrical requirements. It is often encountered in less expensive instruments, and is the commonly used detector for the analysis of fixed gases. Until the introduction of the FID, it was by far the most common detector in use. Unlike the FID, no additional gases (beyond the carrier gas) are required, which makes it useful in situations where hydrogen gas would be hazardous or where additional gas supplies are not readily available. This may be important in field applications where portability is a factor.

For use with capillary columns, the TCD has been engineered down to a small volume in order to accommodate the need for a response time of the detector that is significantly less than the chromatographic peak width. Competing with this desire for small volume is the practical consideration that TC detectors become more sensitive to external effects as cell volume is decreased. A similar trade-off occurs when use of a make-up gas is warranted in order to help sweep the detector clear of sample, because the resultant sample dilution decreases the voltage difference responsible for the detector response. Currently, cell volumes are in the 100 µL range, suitable for use with 530 µm columns without make-up gas. At least one manufacturer offers a cell volume of less than 5 µL, but still recommends the use of make-up gas so that the total flow through the cell is 5 mL min⁻¹. Thus, the narrow-bore capillary columns can be accommodated, albeit with some loss of sensitivity resulting from the dilution.

The TCD responds to bulk properties of the effluent. It compares the conductivity of a filament exposed to the carrier gas to that of a filament exposed to sample components. The baseline is established by heating the filaments to a constant temperature with carrier gas flowing. Since the thermal conductivity of helium or hydrogen (often used as the carrier gas) is higher than virtually any other material likely to be encountered, the temperature of the filament increases when sample components are present in the effluent. The electronics of the TCD adjusts the current to maintain a constant temperature or allow the temperature to rise and respond to the difference in resistance. In either case the resulting voltage is used as the chromatographic signal based on the assumption that other thermal effects remain constant. The filament itself is constructed from tungsten

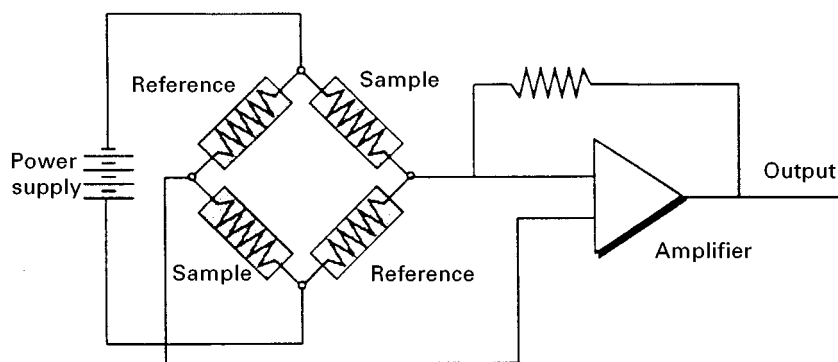


Figure 2 Schematic diagram of thermal conductivity detector electronics.

or tungsten–rhenium alloys to take advantage of the high resistance–temperature coefficient. TCD sensitivity increases as the temperature difference between the filament and the detector wall increases. This, coupled with the desire to have relatively low filament temperature (in order to increase lifetime), means that the detector body temperature should be set as low as possible while still preventing sample components from condensing.

Various detector designs incorporate geometries with as many as four filaments. These are often incorporated into a Wheatstone bridge circuit (Figure 2) and produce a voltage imbalance when an analyte passes through one side. In the HP 5890 series II TCD cell depicted in Figure 3 there is a single filament and a switching system so that the gas stream alternates every 200 ms. The response is due to the voltage difference of a filament exposed

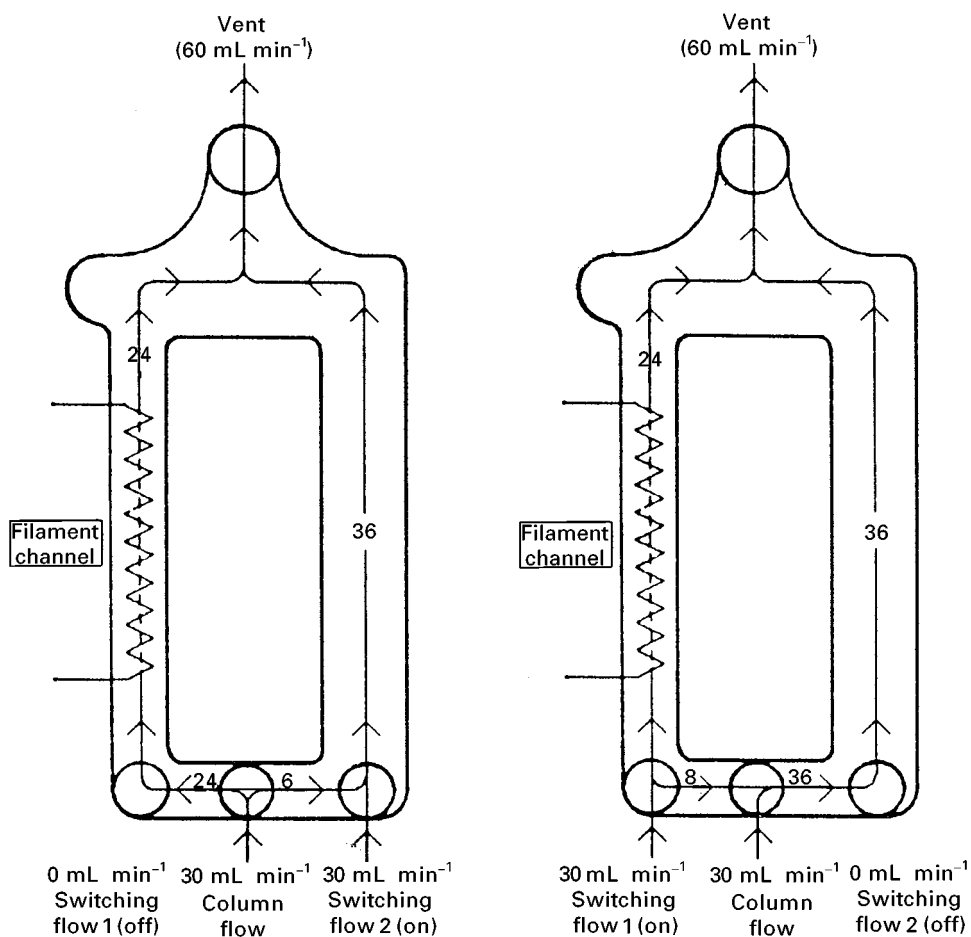


Figure 3 HP 5890 series II thermal conductivity cell.

alternatively to pure carrier gas and carrier gas plus sample.

As mentioned above, He and H₂ are commonly used as carrier gases when the TCD is involved. H₂ has a significantly higher thermal conductivity than does He, but is often not chosen because of its potential explosiveness and because it may reduce the oxide coating on the filament and thus cause changes in response factors. Most sample components have thermal conductivities well below that of either hydrogen or helium (Table 1), thus providing a detector with a universal response. Analysis of hydrogen requires special consideration. For instance, N₂ or Ar could be used as a carrier gas, but then sensitivity to other compounds would be much reduced. Alternatively, He can be used as a carrier gas, and the detector temperature kept relatively high.

The TCD is a concentration-dependent detector, so that the peak size is dependent on flow rates. The MDA is much higher than for the FID, corresponding to about 10 p.p.m. of C₉ in the cell. Although response factors cannot be calculated from thermal conductivities alone, they have been determined for many compounds and shown to vary only slightly within a homologous series. This makes the TCD useful for quantitative work. Organometallic compounds have somewhat low response factors, as do halogenated compounds. Some representative response values, relative to benzene, are shown in Table 1.

Operationally the TCD is quite simple, although the filament can be permanently damaged if current is left on without gas flow being maintained. Likewise,

Table 1 Thermal conductivities and TCD response values for selected compounds

Thermal conductivity of common gases (relative to He = 100) ^a		Molar response (in helium) (relative to benzene = 100)
H ₂	125.3	
He	100	
N ₂	18	
Ar	12.8	
CO ₂	12.7	
Ethane	19.3	51
<i>n</i> -Butane	13.5	85
<i>n</i> -Nonane	10.8	177
<i>i</i> -Butane	14.0	82
Cyclohexane	10.1	114
Benzene	10.4	100
Acetone	9.9	86
Ethanol	12.5	72
Chloroform	5.9	108
Methyl iodide	4.5	96
Ethyl acetate	9.7111	

^aTemperature 100°C.

exposure to traces of oxygen is damaging to the filament, so that the system must be leak-free. Use of plastic tubing such as nylon or polytetrafluoroethylene is discouraged since they are permeable to oxygen. Temperature variations in the detector will result in baseline fluctuations so careful control of heating elements is necessary. When properly operating, the noise level is only a few microvolts.

The design of these two detectors has not changed markedly since their introduction over three decades ago and they are firmly entrenched in chromatographic analyses. This will continue to be the case for systems in traditional laboratories. In addition, there has been recent progress in the development of miniature gas chromatographic systems and fast chromatography. This miniaturization has been driven by advances in field analyses and the concomitant need for portability. These systems take advantage of silicon micro machining and integrated circuit-processing techniques, including a microthermal conductivity detector. More information about this can be obtained from the publication by Etiope (see Further Reading).

See also: II/Chromatography: Gas: Column Technology; Detectors: Mass Spectrometry; Detectors: Selective; Historical Development; Theory of Gas Chromatography. III/Gas Analysis: Gas Chromatography.

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